REMARKS

An Abstract has been added to the Specification. Support for the Abstract can be found in the Specification as filed. No new matter has been introduced herewith.

Claim 29 has been canceled. Claims 8, 14, 15, and 22 have been amended. Support for the amendments can be found in the Specification and original Claims as filed. More specifically, support for the amendments to Claim 8 can be found, for example, in the original Claim 1 as filed. Support for the amendments to Claim 14 can be found in the Specification as filed for example, on page 20, lines 17-24. Support for the amendments to Claim 22 can be found in the Specification as filed, page 31 lines 23-32.

New Claims 33-36 have been added to better define patentable subject matter. Support for the new claims can be found in the Specification as filed. More specifically, support for Claims 33 and 34 can be found in the original claim 3 and in the Specification, Tables 1 and 2. Support for Claim 35 can be found in the original claim 7 and on page 21 lines 1-5. Support for Claim 36 can be found in the Specification on page 3 lines 8-24, and on page 6 lines 18-26.

No new matter is being added herewith.

Rejections under 35 U.S.C. §101

The Examiner rejected Claim 14 under 35 U.S.C. §101 as directed to a non-statutory subject matter in reciting an "animal" that would encompass humans. The Applicants have amended Claim 14 to now recite "mouse or rat". Support can be found in canceled Claim 29. Accordingly, the Applicants respectfully request withdrawal of this §101 rejection of Claim 14.

The Examiner rejected Claim 22 under 35 U.S.C. §101 as directed to a non-statutory subject matter in reciting a "descendent of the transgenic animal" which can be a normal animal, therefore a product of nature. The Applicants have amended Claim 22 to now additionally recite that "descendant of the transgenic mouse or rat comprises a mutant mouse parkin2 protein or a homologue thereof". Accordingly, the Applicants respectfully request withdrawal of this §101 rejection of Claim 22.

Rejections under 35 U.S.C. §112, first paragraph.

The Examiner rejected Claims 8, 14, 15, 22, and 29 under 35 U.S.C. §112, first paragraph, as lacking an enabling disclosure and failing to provide an adequate written description. Specifically, the Examiner indicated that the specification only teaches a method to

make a transgenic parkin2 knockout mouse having an exon3 deletion. The Examiner also asserts that the specification does not teach whether the transgenic parkin2 knockout mouse would exhibit phenotypes associated with symptoms of Parkinson's disease.

Applicants respectfully suggest that the teaching of the specification as filed is much broader than a transgenic parkin2 knockout mouse having an exon3 deletion. Indeed, Tables 1 and 2 (pages 18-19 of the specification as filed) describe many other specific mutations that are included within the scope of the present invention. Further, the specification teaches that "...for the creation of an animal model according to the present invention, each polynucleotide sequence can be used, containing mutations, insertions or deletions which are known to cause Parkinson's disease in a human, when they occur in the corresponding human sequence." (See page 17, lines 17-20). Furthermore, the specification sets forth a list of such mutations in the human parkin2 gene, that are known to be associated with symptoms of Parkinson's disease in humans (see page 3, lines 8-24 of the specification as filed). The human parkin2 gene consists of 12 exons and encodes a 465 amino acid protein. The Applicants disclose a mouse parkin2 gene which also consists of 12 exons and encodes a 464 amino acid protein. In addition to the homologous structural organization between the human and mouse parkin2 genes, they also share greater than 80% sequence homology (see Figure 1 of the specification as filed). Accordingly, because the disclosed mutations to the human parkin2 gene are known to cause symptoms of Parkinson's disease, and because the human and mouse parkin2 gene share substantial structural homology, Applicants respectfully assert that one skilled in the art would: (1) understand that Applicants were in possession of the recited invention, and (2) be enabled to make the recited transgenic mouse or rat carrying a mutation in the parkin2 gene, with an expectation that such a mutation would be associated with symptoms of Parkinson's disease, analogous to corresponding situation in humans.

The Examiner also expressed concern that without teaching from the specification, one skilled in the art would have to turn to the prior art for guidance to make and use the recited transgenic animals. Applicants respectfully remind the Examiner that "[t]he law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention." *S3 Inc. v. nVIDIA Corp.*, 259 F.3d 1364, 59 USPQ2d 1745 (Fed. Cir. 2001) (*emphasis added*).

Furthermore, Applicants have not merely relied on the skill of those in the art, but have specifically set forth in the specification, the relevant teachings of the prior art, regarding the clear relationship between certain identified mutations in the human parkin2 gene and symptoms of Parkinson's disease. Thus, because Applicants have identified mutations in the mouse parkin2 gene, which correspond to mutations in the homologous human parkin2 gene and are known to cause symptoms of Parkinson's disease, Applicants respectfully assert that they have provided an enabling disclosure for a person skilled in this field, with knowledge of the relationship between specific mutations and the associated phenotype in humans.

The Examiner also expressed concern regarding enablement of transgenic animals that "exhibit no phenotype or that exhibit transgenic-dependent phenotypes other than that of symptoms of Parkinson's disease...". The Examiner suggested that phenotype would be unpredictable because the claims encompass both heterozygous and homozygous animals. Applicant respectfully disagrees. The claims as amended encompass only animals expressing the disease phenotype (and not phenotypes other than symptoms of Parkinson's disease). Further, although the amended claims do not expressly limit the animals to a particular genotype, the claims do expressly recite a transgenic animal... comprising a mutation, wherein said mutation causes symptoms of Parkinson's disease in humans. Further, the specification (see e.g., page 2, beginning at line 25) teaches that Parkinson's disease phenotype linked to mutations in the human parkin2 gene (structurally analogous to Applicant's mouse parkin2 gene) is expressed as an autosomal recessive trait in humans. Although the Examiner indicated (based on Wall, 1996) that consequences of transgene products are not always accurately predicted in transgenic mouse studies, the non-specific, somewhat outdated teachings of Wall fail to address Applicant's recited invention, where a clear structure-function relationship among the parkin2 gene mutations (in humans and mice) and the disease phenotype (in humans) is known and renders predictable the consequence of the homologous transgene products in mice. Thus, Applicants respectfully assert that they have provided sufficient guidance to enable the skilled practitioner to make and use the recited transgenic animal within the scope of the claims.

With regard to the mammal species for generation of transgenic animals, Applicants have amended the claims to recite only mice and rats. Applicant respectfully asserts that theses rodent species share sufficient genetic similarities and embryonic stem cell availability (Mullins, J.J. *et*

al. 1990 "Fulminant hypertension in transgenic rats harbouring the mouse Ren-2 gene" *Nature* 1990 **344(6266)**:541; Breban M. 1998 "HLA-B27 transgenic rats model" *Ann Med Interne* **149(3)**:139-41; Hooper, M.L. 1992 "Embryonal Stem Cells: Introducing Planned Changes into the Animal Germline" Harwood Academic Publishers Philadelphia SCIENCE Book Stacks; Capecchi, M.R. 1994 "Targeted Gene Replacement" *Sci Am* pp. 52-59; DePamphilis M.L. *et al.* 1988 "Microinjecting DNA into mouse ova to study DNA replication and gene expression and to produce transgenic animals" *Biotechniques* **6**:662-680) to enable the recited claims as amended. We will provide the hard copies of the recited references for the Examiner's convenience under a separate cover.

In conclusion, Applicants respectfully assert that the skilled practitioner would be able to make and use the recited transgenic mouse or rat (or descendants thereof) based on the teaching of the specification without undue experimentation. Applicant points out that the level of skill in this art is very high (one of the Wands factors which the Examiner did not address), that the highly skilled practitioner is familiar with the prior art (e.g., the correlation between specific parkin2 mutations and disease phenotype in humans), and that some experimentation (e.g., verifying the species parallel structure-phenotype correlation) does not necessarily constitute undue experimentation—where as here, the specification provides adequate guidance. Accordingly, Applicants respectfully request reconsideration and withdraw of the enablement and written description rejections under §112, first paragraph of Claims 8, 14, 15, and 22 (Claim 29 has been canceled).

Rejections under 35 U.S.C. §112, second paragraph.

The Examiner rejected Claims 8, 14, 15, 22, and 29 under 35 U.S.C. §112, second paragraph as being indefinite.

Specifically, Claims 8, 15, 22, and 29 were considered indefinite in recitation of "...a mutant parkin2 protein...wherein said mutant causes symptoms of Parkinson's disease". The Applicants have amended independent claims 8 and 14 to now recite "...mutant mouse parkin2 protein...comprising a mutation, wherein said mutation causes symptoms of Parkinson's disease when said mutation is present in a human polynucleotide homologous to a polynucleotide of SEQ ID NO: 1". The Applicants assert that this amendment renders the claims definite.

Claim 22 was considered indefinite in recitation "said animal". The Applicants have amended the claim to now recite "said descendant".

Claim 14 was considered indefinite for being incomplete by omitting the steps describing how the pseudopregnant female animal produces the transgenic animal comprising a mutant parkin2 gene. The Applicants have amended the claim to add these steps. Support for this amendment can be found in the Specification as filed, page 20 lines 17-19. However, the Applicants also would like to point out that the production of a transgenic animal after the introduction of a blastocyst into a pseudopregnant female is known and within the skill of a person of ordinary skill in the art.

Claims 22 and 29 were considered indefinite in recitation of "transgenic animal" that had not antecedent basis in the parent Claim 8. The Applicants have canceled Claim 29, and amended Claim 22 to now recite "transgenic mouse or rat" that has a proper antecedent basis in Claim 8 as amended herein.

Accordingly, the Applicants respectfully request withdrawal of this §112 rejection of Claims 8, 14, 15, and 22.

Rejections under 35 U.S.C. §102(b).

The Examiner rejected Claim 22 under 35 U.S.C. §102(b) as being allegedly anticipated by Allet *et al.* Allen *et al.* disclose a wild type mouse. Claim 22 recited a descendant of the transgenic animal that can be a wild-type, and therefore was anticipated by Allen *et al.* The Applicants have amended the Claim 22 to now additionally recite "wherein said descendant of the transgenic mouse or rat comprises a mutant mouse parkin2 protein or a homologue thereof". The Applicants assert that the current amendment makes Claim 22 novel over Allen *et al.*

Accordingly, the Applicants respectfully request withdrawal of this §102 rejection of Claim 22.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action are no longer sustainable with regard to the amended claims. Accordingly, Applicants request the expeditious allowance of the pending claims.

The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, id any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully invited to call undersigned at (949) 721-6323 (direct line), to discuss such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 4/25/03

By: _____

Mark R. Benedict
Registration No. 44,531
Attorney of Record
Customer No. 20,995
(949) 760-0404

O:\DOCS\MXG\MXG-2319.DOC
042303